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(54) Title: METALLOPROTEINASE INHIBITORS

(57) Abstract

2S–{[(5–Dimethylaminonaphthalene–1–sulfonyl)–methyl–amino]–methyl}–5–methyl–3R–(morpholine–4–carbonyl)–hexanoic acid hydroxyamide and similar compounds are matrix metalloproteinase inhibitors.

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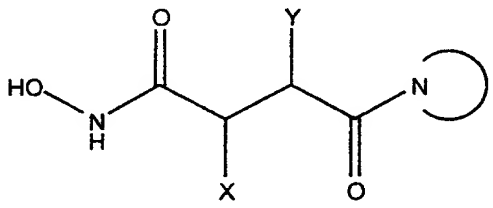
Known classes of collagenase inhibitors include those disclosed in EP-A-0574758 (Roche), EP-A-0684240 (Roche), and WO 95/33731 (Roche). In general, the compounds disclosed in those publications may be represented by the structural formula (IA)



(IA)

in which X, Y and the N-containing ring are variable in accordance with the specific disclosures of the publications.

Brief Description of the Invention

Our copending international patent application PCT/GB97/02891 (the disclosures of which are hereby incorporated by reference) made available a novel class of compounds which are inhibitors of matrix metalloproteinases. The present invention provides additional members of the class of compounds disclosed in PCT/GB97/02891, but which were not specifically identified or exemplified therein. In general, as members of the class disclosed in PCT/GB97/02891, the present compounds are selective inhibitors of collagenases, such as human fibroblast collagenase, over gelatinases, stromelysins and matrilysin, and are therefore indicated for treatment of diseases primarily mediated by collagenases.

The present compounds conform to general formula (IA), but differ in structure from prior art compounds of that general formula principally in the identity of the group X. In the compounds of the present invention, the group X is a sulfonamidoalkyl group, not contemplated by any of EP-A-0574758, EP-A-0684240, or WO 95/33731.

Detailed Description of the Invention

Metalloproteinase Inhibitors

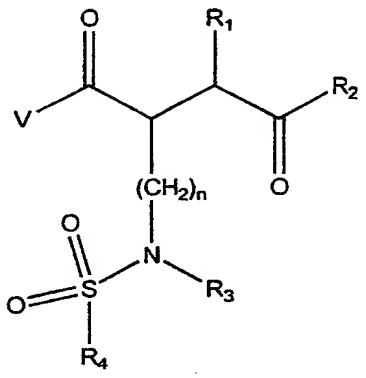
The present invention relates to therapeutically active hydroxamic and carboxylic acid derivatives, to processes for their preparation, to pharmaceutical compositions containing them, and to the use of such compounds in medicine. In particular, the compounds are inhibitors of matrix metalloproteinases involved in tissue degradation, especially collagenases such as human fibroblast collagenase (MMP-1), human neutrophil collagenase (MMP-8) and collagenase-3 (MMP-13).

Background to the Invention

Compounds which have the property of inhibiting the action of metalloproteinases involved in connective tissue breakdown such as collagenases, stromelysins and/or gelatinases (known as "matrix metalloproteinases", and herein referred to as MMPs) are thought to be potentially useful for the treatment or prophylaxis of conditions involving such tissue breakdown, for example rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, corneal epidermal or gastric ulceration, and tumour metastasis, invasion and growth. MMP inhibitors are also of potential value in the treatment of neuroinflammatory disorders, including those involving myelin degradation, for example multiple sclerosis, as well as in the management of angiogenesis dependent diseases, which include arthritic conditions and solid tumour growth as well as psoriasis, proliferative retinopathies, neovascular glaucoma, ocular tumours, angiofibromas and hemangiomas. However, the relative contributions of individual MMPs in any of the above disease states is not yet fully understood.

Metalloproteinases are characterised by the presence in the structure of a zinc(II) ionic site. It is now known that there exists a range of metalloproteinase enzymes that includes human fibroblast collagenase (MMP-1), human neutrophil collagenase (MMP-8) and collagenase-3 (MMP-13), 72 kDa-gelatinase, 92 kDa-gelatinase, stromelysin-1, stromelysin-2 and PUMP-1 (J.F. Woessner, FASEB J, 1991, 5, 2145-2154).

According to PCT/GB97/02891 there is provided a compound of formula (I)



(I)

wherein

V is HO- or HONH-

n is 1, 2, 3 or 4;

R_1 is a C_1-C_{12} alkyl,
C_2-C_{12} alkenyl,
C_2-C_{12} alkynyl,
perfluoroalkyl,
phenyl(C_1-C_6 alkyl)-,
heteroaryl(C_1-C_6 alkyl)-,
non-aryl heterocyclyl(C_1-C_6 alkyl)-,
cycloalkyl(C_1-C_6 alkyl)-,
cycloalkenyl(C_1-C_6 alkyl)-,
phenoxy(C_1-C_6 alkyl)-,
heteroaryloxy(C_1-C_6 alkyl)-,
phenyl(C_1-C_6 alkyl)O(C_1-C_6 alkyl)-,
heteroaryl(C_1-C_6 alkyl)O(C_1-C_6 alkyl)-,
phenyl(C_1-C_6 alkyl)S(C_1-C_6 alkyl)- or
heteroaryl(C_1-C_6 alkyl)S(C_1-C_6 alkyl)- group,

any one of which may be optionally substituted by C_1-C_6 alkyl, trifluoromethyl, C_1-C_6 alkoxy, hydroxy, halo, cyano (-CN), phenyl, substituted phenyl or heteroaryl;

R_2 is a saturated 5- to 8-membered monocyclic or bridged N-heterocyclic ring which is attached via the N atom and which, when it is monocyclic, (i) optionally contains as a ring member O, S, SO, SO_2, or NR_5 wherein R_5 is hydrogen, hydroxy, C_1-C_6 alkyl, (C_1-C_6 alkoxy)C_1-C_6 alkyl, benzyl, acyl, an amino protecting group, or a group $-SO_2R_6$ wherein R_6 is C_1-C_6 alkyl or a substituted or unsubstituted phenyl or heteroaryl group, and/or (ii) is optionally substituted on one or more C atoms by hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano, oxo, ketalised oxo, amino, mono(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, carboxy, C_1-C_6 alkoxycarbonyl, hydroxymethyl, C_1-C_6 alkoxymethyl, carbamoyl, mono(C_1-C_6 alkyl)carbamoyl, di(C_1-C_6 alkyl)carbamoyl, or hydroxyimino;

R_3 is hydrogen, C_1-C_6 alkyl, benzyl, acyl, an amino protecting group, or a group $-(CH_2)_mCOZ$ where m is an integer from 1 to 6, and Z represents OH, C_1-C_6 alkoxy or $-NR_xR_y$ where R_x, R_y each independently represent hydrogen or C_1-C_6 alkyl; and

R_4 is optionally substituted

C_1-C_6 alkyl,
C_2-C_6 alkenyl,
C_2-C_6 alkynyl,
C_1-C_3 perfluoroalkyl,
cycloalkyl,
cycloalkyl(C_1-C_6 alkyl)-,
cycloalkenyl,
cycloalkenyl(C_1-C_6 alkyl)-,
di-(C_1-C_6 alkyl)amino,

phenyl,
phenyl(C_1-C_6 alkyl)-,
biphenyl,
phenyl-heteroaryl,
naphthyl,
non-aryl heterocyclyl,
non-aryl heterocyclyl(C_1-C_6 alkyl)-,
heteroaryl or
heteroaryl(C_1-C_6 alkyl)-;
heteroaryl-phenyl;
heteroaryl-heteroaryl;
aryloxyaryl or

R_3 and R_4 taken together represent a divalent C_3-C_6 alkylene or alkenylene group which may optionally be (i) substituted by an oxo group, and/or (ii) substituted by (C_1-C_6)alkoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), cyano, trifluoromethyl, nitro, -COOH, -$CONH_2$, -$CONHR^A$ or -$CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group, and/or (iii) fused to a phenyl or heteroaryl group which itself may be substituted;

and pharmaceutically acceptable salts hydrates and solvates thereof.

According to the present invention there is provided a compound which is a member of the group consisting of :

2S-{[(5-Dimethylaminonaphthalene-1-sulfonyl)-methyl-amino]-methyl}-5-methyl-3R-(morpholine-4-carbonyl)-hexanoic acid hydroxyamide

3R-Cyclopentylmethyl-N-hydroxy-2S-[(methanesulfonyl-methyl-amino)-methyl)]-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-[(methanesulfonyl-methyl-amino)-methyl)]-4-morpholin-4-yl-4-oxo-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-{[(4-benzenesulfonyl)-methyl-amino]-methyl}-4-oxo-4-piperidine-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-{[(4-benzenesulfonyl)-methyl-amino]-methyl}-4-morpholin-4-yl-4-oxo-butyramide

2S-[(Methanesulfonyl-methyl-amino)-methyl]-5-methyl-3R-(morpholine-4-carbonyl)-hexanoic acid hydroxyamide

2S-{[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-methyl}-5-methyl-3R-(morpholine-4-carbonyl)-hexanoic acid hydroxyamide

2S-{[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-methyl}-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid hydroxyamide

3R-Cyclopentylmethyl-2S-{[ethyl-(4-methoxy-benzenesulfonyl)-amino]-methyl}-N-hydroxy-4-oxo-4-morpholine-1-yl-butyramide

3R-Cyclopentylmethyl-2S-{[ethyl-(4-methoxy-benzenesulfonyl)-amino]-methyl}-N-hydroxy-4-morpholine-4-yl-4-oxo-butyramide

3R-Cyclopentylmethyl-2S-{[(5-dimethyamino-naphthalene-1-sulfonyl)-methyl-amino]-methyl}-N-hydroxy-4-oxo-4-piperidine-1-yl-butyramide

3R-Cyclopentylmethyl-2S-{[(5-dimethyamino-naphthalene-1-sulfonyl)-methyl-amino]-methyl}-N-hydroxy-4-morpholine-4-yl-4-oxo-butyramide

2S-{[(5-Dimethylaminonaphthalene-1-sulfonyl)-ethyl-amino]-methyl}-5-methyl-3R-(morpholine-4-carbonyl)-hexanoic acid hydroxyamide

2S-{[(5-Dimethylaminonaphthalene-1-sulfonyl)-methyl-amino]-methyl}-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid hydroxyamide

3R-Cyclopentylmethyl-2S-[(ethanesulfonyl-methyl-amino)-methyl]-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-{[methyl-(propane-2-sulfonyl]-amino]-methyl}-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-{[methyl-(octane-1-sulfonyl)-amino]-methyl}-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-[(methyl-trifluoromethanesulfonyl-amino)-methyl]-4-oxo-4-piperidin-1-yl-butyramide

2S-{[(4-Chloro-benzenesulfonyl)-methyl-amino]methyl}-3R-cyclopentylmethyl-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-{[methyl-(quinoline-8-sulfonyl)-amino]-methyl}-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-{[methyl-(naphthalene-1-sulfonyl)-amino]-methyl}-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-{[(isoquinoline-5-sulfonyl)-methyl-amino]-methyl}-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-2S-{[(6-dimethylamino-naphthalene-1-sulfonyl)-methyl-

amino]-methyl}-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-2S-{[dimethylsulfamoyl-methyl-amino]-methyl}-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide

2S-[(Butyl-methanesulfonyl-amino)-methyl]-3R-cyclopentylmethyl-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-[(isopropyl-methanesulfonyl)-amino)-methyl]-4-oxo-4-piperidin-1-yl-butyramide

2S-[(*tert*-Butyl-methanesulfonyl)-amino)-methyl]-3R-cyclopentylmethyl-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-[(cyclopropyl-methanesulfonyl)-amino)-methyl]-4-oxo-4-piperidin-1-yl-butyramide

2S-[(Cyclopentyl-methanesulfonyl)-amino)-methyl]-3R-cyclopentylmethyl-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide

and pharmaceutically acceptable salts hydrates and solvates thereof.

Compounds of the invention may be prepared as described in the Examples herein.

As mentioned above, the present compounds are useful in human or veterinary medicine since they are active as inhibitors of MMPs. Enzyme inhibition assays useful for determining the activity of a particular compound of the invention against MMPs are known, see for example the assays described in Biological Example A below, and the MMP inhibition assays described in patent publications listed above in the section "Background to the Invention".

Accordingly in another aspect, this invention concerns:

(i) a method of management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs in mammals, in particular in humans, which method comprises administering to the mammal an effective amount of a compound which is a member of the group defined above, or a pharmaceutically acceptable salt thereof; and

(i) a compound which is a member of the group defined above, for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMP; and

(iii) the use of a compound which is a member of the group defined above in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs.

Diseases or conditions mediated by MMPs include those involving tissue breakdown such as bone resorption, inflammatory diseases, dermatological conditions and tumour invasion by secondary metastases, in particular rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration and tumour invasion by secondary metastases as well as neuroinflammatory disorders, including those involving myelin degradation, for example multiple sclerosis.

In a further aspect of the invention there is provided a pharmaceutical or veterinary composition comprising a compound which is a member of the group defined above together with a pharmaceutically or veterinarily acceptable excipient or carrier.

It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular

disease undergoing therapy. Optimum dose levels and frequency of dosing will be determined by clinical trial.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

For topical application to the eye, the drug may be made up into a solution or suspension in a suitable sterile aqueous or non aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edeate; preservatives including bactericidal and fungicidal agents such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

The following Preparative Examples A, B and C describe the synthetic procedures used for the preparation of the compounds of the invention. The products of Preparative Examples A, B and C are disclosed in PCT/GB97/02891. Examples 1-29 relate to compounds of the present invention.

The following abbreviations have been used throughout:

DMF	N,N-Dimethylformamide
EDC	N-Ethyl-N'-(3-dimethylaminopropyl)-carbodiimide
HOBt	1-Hydroxybenzotriazole
THF	Tetrahydrofuran

^{1}H and ^{13}C NMR spectra were recorded using a Bruker AC 250E spectrometer at 250.1 and 62.9 MHz, respectively. Elemental microanalyses were performed by Medac Ltd. (Brunel Science Park, Cooper's Hill Lane, Englefield Green, Egham, Surrey TW20 0JZ). Preparative HPLC was performed using an Gilson automated preparative HPLC system. Electrospray mass spectrometry was performed using a PE-Sciex AP 165 system with a turbo ion spray interface. Infra-red spectra were obtained with a Perkin Elmer 1600 FTIR instrument using a reflection disc.

Preparative Example A

2S-[3-(4-Methoxybenzenesulfonyl-amino)-propyl]-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid hydroxyamide

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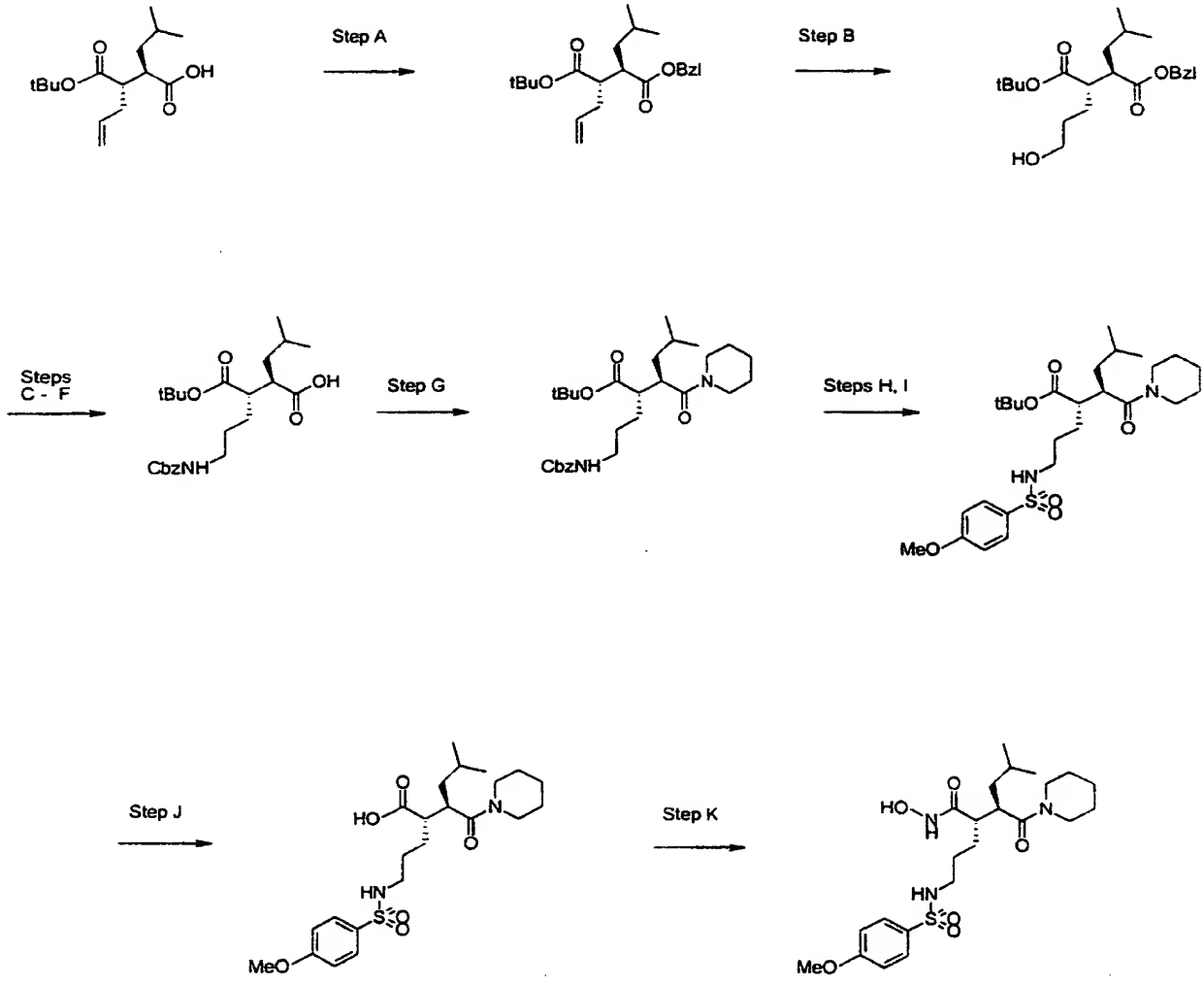
The title compound was prepared according to the route outlined in Scheme 1 and is described in detail below.

Scheme 1



Reagents and conditions: (A) Bzl-Br, K_2CO_3 in acetone; (B) 9-BBN, H_2O_2 in THF; (C) MsCl, Et_3N in THF, 0°C; (D) NaN_3, $^nBu_4I$, in toluene/water, reflux; (E) H_2,10% Pd/C in ethanol; (F) Z-ONSu, Et_3N, THF; (G) piperidine EDC, HOBt, THF; (H) H_2, 10% Pd/C in ethanol; (I) 4-MeO(C_6H_4)SO_2Cl, Et_3N in THF; (J) TFA in CH_2Cl_2, 4°C; (K) HOBt, EDC in DMF, then $H_2NOH.HCl$, NMM.

Step A: 2S-Allyl-3R-isobutyl-succinic acid 4-benzyl ester 1-tert-butyl ester

2S-Allyl-3R-isobutyl-succinic acid 1-tert-butyl ester dicyclohexylamine salt (31.6 g, 70 mmol) was partitioned between dichloromethane and 1M hydrochloric acid. The organic phase was washed with water, dried, filtered and concentrated to dryness. The resulting free acid (18.6 g) was dissolved in acetone (250 ml) and the solution was placed under an argon atmosphere. Potassium carbonate (19 g, 138 mmol) and benzyl bromide (7.4 ml, 62.2 mmol) were added and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the residual oil was dissolved in ethyl acetate. The solution was washed with water (3 x 50 ml), dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated to dryness and the residue was purified by flash chromatography (silica gel, ethyl acetate hexane, 1:9) to provide the title compound as a colourless oil (21.7 g, 88%). ^{1}H-NMR: δ ($CDCl_3$), 7.41 - 7.30 (5H, m), 5.70 (1H, m), 5.14 (2H, d, J = 1.3 Hz), 5.06 -4.94 (2H, m), 2.75 (1H, m), 2.60 (1H, m), 2.45 (1H, m), 2.12 (1H, m), 1.71 (1H, m), 1.43 (9H, s), 1.32 - 1.11 (2H, m), 0.88 (3H, d, J = 6.5 Hz) and 0.86 (3H, d, J = 6.6 Hz)

Step B: 2S-(3-Hydroxypropyl)-3R-isobutyl-succinic acid 4-benzyl ester 1-tert-butyl ester

2S-Allyl-3R-isobutyl-succinic acid 4-benzyl ester 1-tert-butyl ester (7.42 g, 20.6 mmol) was dissolved in a 0.5M solution of 9-BBN in THF (100 ml, 50 mmol) at room temperature and allowed to stir for 3 days. The solution was treated with 3M sodium hydroxide solution (10 ml, 30 mmol) followed by 30% w/v hydrogen peroxide (slowly) and the reaction mixture was allowed to stir for a further 2 hours. THF was evaporated under reduced pressure and the residue was diluted with ethyl acetate (100 ml) and water (50 ml). The organic layer was separated, washed with water (3 x 50 ml), dried over anhydrous sodium sulfate and filtered. Concentration under reduced pressure gave an oil which was purified by flash chromatography (silica gel,

ethyl acetate-hexane, 3:7). Colourless oil (5.3 g, 68%).

Step C: 3R-Isobutyl-2S-(3-methanesulfonyloxy-propyl)-succinic acid 4-benzyl ester 1-tert-butyl ester

2S-(3-Hydroxypropyl)-3R-isobutyl-succinic acid 4-benzyl ester 1-tert-butyl ester (5.3 g, 14 mmol) was dissolved in dry THF (150 ml) and the solution was cooled to 0°C. Triethylamine (2.1 ml, 15.1 mmol) was added followed by methanesulfonyl chloride (1.2 ml, 15.5 mmol) and the reaction mixture was allowed to warm slowly to room temperature before stirring overnight. The solvents was removed under reduced pressure and the residue was dissolved in ethyl acetate (150 ml). The organic solution was washed with water (3 x 50 ml), dried over anhydrous sodium sulfate and filtered and concentrated *in vacuo* to leave the title compound (6.1 g, 95%) which was used without further purification.

Step D: 2S-(3-Azido-propyl)-3R-isobutyl-succinic acid 4-benzyl ester 1-tert-butyl ester

3S-Isobutyl-2R-(3-methanesulfonyloxy-propyl)-succinic acid 4-benzyl ester 1-tert-butyl ester (6.1 g, 14 mmol) was dissolved in toluene (100 ml) and tetrabutylammonium iodide (4.9 g, 14 mmol) was added followed by a solution of sodium azide (8.7 g, 140 mmol) in water (100 ml). The reaction mixture was heated at reflux for 8 hours, stirred at room temperature for 3 days then heated at reflux for a further 6 hours. The reaction mixture was diluted with ethyl acetate (100 ml) and the organic layer was separated, washed with water (3 x 80 ml), dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The product thus obtained (5.5 g, 95%) was used without further purification.

Step E: 2S-(3-Amino-propyl)-3R-isobutyl-succinic acid 1-tert-butyl ester

2S-(3-Azido-propyl)-3R-isobutyl-succinic acid 4-benzyl ester 1-tert-butyl ester (5.5 g, 12.7 mmol) was dissolved in ethanol (100 ml) and the solution was placed under an argon atmosphere. 10% Palladium on charcoal (800 mg) was added and hydrogen was introduced by bubbling into the suspension. The reaction mixture was stirred overnight under an atmosphere of hydrogen. The system was purged with argon and the catalyst was removed by filtration. The solution was concentrated *in vacuo*, whereupon ^{1}H-NMR analysis revealed that the reaction was incomplete. Hydrogenolysis was repeated exactly as described above to provide the title compound as an amorphous solid (3.7 g, ca. quant.). ^{1}H-NMR: δ ($CDCl_3$), 5.19 - 4.85 (2H, br s), 3.17 - 2.93 (2H, m), 2.69 (1H, m), 2.44 (1H, m), 1.89 - 1.40 (6H, m), 1.46 (9H, s), 1.12 (1H, m), 0.89 (3H, d, J = 6.2 Hz) and 0.88 (3H, d, J = 6.2 Hz).

Step F: 2S-(3-Benzyloxycarbonylamino-propyl)-3R-isobutyl-succinic acid 1-tert-butyl ester

2S-(3-Amino-propyl)-3R-isobutyl-succinic acid 1-tert-butyl ester (3.7 g, 12.9 mmol) was dissolved in THF (150 ml) and the solution was cooled to 0°C. Triethylamine (3.8 ml, 27.3 mmol) and Z-ONSu (3.5 g, 14 mmol) were added and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (150 ml), washed successively with 1M hydrochloric acid (50 ml) and water (2 x 30 ml) dried over anhydrous sodium sulfate and filtered. Concentration under reduced pressure afforded the title compound contaminated with excess Z-ONSu, which could not be separated by column chromatography or acid-base extraction. The crude mixture was therefore dissolved in THF (100 ml) and treated with N,N-dimethylethylenediamine (0.18 ml, 1.6 mmol) with stirring overnight at room temperature. The by-products were then conveniently removed by acid extraction from ethyl acetate, to leave the pure title compound (2.43 g, 66%) after removal of solvent.

Step G: 2S-(3-Benzyloxycarbonylamino-propyl)-5-methyl-3R-(piperidine-1-carbonyl)-

hexanoic acid tert-butyl ester

2S-(3-Benzyloxycarbonylamino-propyl)-3R-isobutyl-succinic acid 1-tert-butyl ester (2.43 g, 5.8 mmol) was dissolved in DMF (150 ml) and the solution was cooled to 0°C before the addition of HOBt (0.9 g, 6.6 mmol) and EDC (1.3 g, 6.8 mmol). The reaction was stirred for 1 hour, after which piperidine (1.1 ml, 11.1 mmol) was added and stirring continued overnight. The solvent was removed in vacuo and the title compound was isolated by extraction followed by flash chromatography (silica gel, ethyl acetate-hexane, 4:6). Colourless oil (2.34 g, 83%).

Step H: 2S-(3-Amino-propyl)-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid tert-butyl ester

2S-(3-Benzyloxycarbonylamino-propyl)-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid tert-butyl ester (2.34 g, 4.8 mmol) was Z-deprotected by hydrogenolysis as described in Step E to provide the title compound as a colourless oil (1.70 g, quant.).

Step I: 2S-[3-(4-Methoxybenzenesulfonyl-amino)-propyl]-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid tert-butyl ester

2S-(3-Amino-propyl)-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid tert-butyl ester (1.70 g, 4.8 mmol) was converted to the title sulfonamide by a similar method to that described in Step C, substituting 4-methoxybenzenesulfonyl chloride for methanesulfonyl chloride. The desired product was isolated as a colourless gum (1.53 g, 61%) by extraction followed by flash chromatography (silica gel, ethyl acetate-hexane, 6:4).

Step J: 2S-[3-(4-Methoxybenzenesulfonyl-amino)-propyl]-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid

2S-[3-(4-Methoxybenzenesulfonyl-amino)-propyl]-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid tert-butyl ester (1.53 g, 2.9 mmol) was dissolved in dichloromethane (15 ml) and TFA (15 ml) was added. The reaction mixture was stored at 4°C overnight. The solvent was removed under reduced pressure and residual TFA was removed by azeotroping with toluene followed by diisopropyl ether. The resulting white waxy solid was used in Step K without further purification (1.37 g, contains residual solvent).

Step K: 2S-[3-(4-Methoxybenzenesulfonyl-amino)-propyl]-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid hydroxyamide

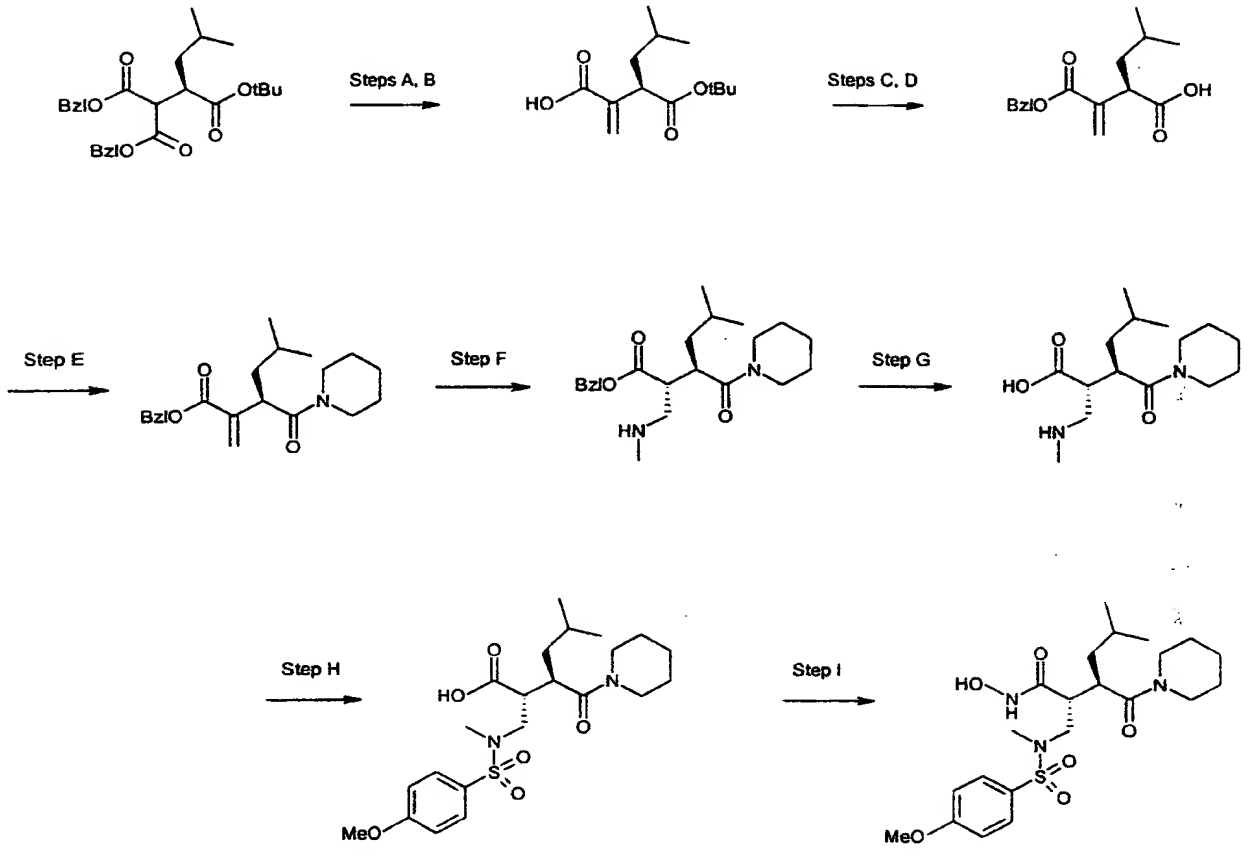
2S-[3-(4-Methoxybenzenesulfonyl-amino)-propyl]-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid (2.9 mmol) was dissolved in DMF (25 ml) and the solution was cooled to 0°C before addition of HOBt (0.6 g, 4.4 mmol) and EDC (0.85 g, 4.4 mmol). The reaction mixture was stirred for 30 minutes after which hydroxylamine hydrochloride (0.4 g, 5.7 mmol) and NMM (0.64 ml, 5.9 mmol) were added. The reaction mixture was allowed to warm to room temperature and then stirred for 3 days. The solvent was removed *in vacuo* and the residue was partitioned between dissolved in ethyl acetate and water. The organic layer was washed successively with sat. aq. sodium hydrogen carbonate and water, dried over anhydrous sodium sulfate and filtered and concentrated under reduced pressure. The desired product was isolated by flash chromatography (acid-washed silica gel, 5% methanol in dichloromethane) followed by extraction to remove remaining traces of HOBt. Colourless gum (300 mg, 21%).

Preparative Example B

2S-{[(4-Methoxybenzenesulfonyl)-methyl-amino]-methyl}-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid hydroxyamide

The title compound was prepared according to the route outlined in Scheme 2 and is described in detail below.

Scheme 2



Reagents and conditions: (A) H_2, 10% Pd/C in EtOAc; (B) piperidine aq. HCHO in ethanol; (C) Bzl-Br, K_2CO_3 in acetone; (D) TFA, CH_2Cl_2, 4°C; (E) piperidine, EDC, HOBt in EtOAc; (F) $MeNH_2$ in methanol; (G) H_2, 10% Pd/C in ethanol; (H) 4-MeO(C_6H_4)SO_2Cl, Et_3N in THF; (I) HOBt, EDC in DMF, then $H_2NOH.HCl$, NMM.

Step A: 2-Carboxy-3R-isobutyl-succinic acid 4-tert-butyl ester

2-Benzyloxycarbonyl-3R-carboxy-5-methyl-hexanoic acid 1-benzyl ester 4-tert-butyl ester (55.53 g, 126 mmol) was dissolved in ethyl acetate (500 ml) and subjected to hydrogenolysis in the presence of 10% palladium on charcoal (5.55 g) under conditions similar to those described in Example 1, Step E. After 3 days TLC analysis indicated that deprotection was complete. The catalyst was removed by filtration and the solution was concentrated under reduced pressure to leave the title compound as a clear oil (ca. 33 g, quant.), which was used without further purification. ^{1}H-NMR: δ ($CDCl_3$), 3.73 (1H, d, J = 9.1 Hz), 3.09 (1H, m), 1.75 - 1.58 (2H, m), 1.45 (9H, s), 1.31 (1H, m), 0.96 (3H, d, J = 6.5 Hz) and 0.92 (3H, d, J = 6.5Hz).

Step B: 3R-Isobutyl-2-methylene-succinic acid 4-tert-butyl ester

2-Carboxy-3R-isobutyl-succinic acid 4-tert-butyl ester (33 g, 126 mmol) was dissolved in ethanol (300 ml) and the solution was cooled in an ice bath during dropwise addition of piperidine (14.95 ml, 151 mmol) followed by 37% aqueous formaldehyde solution (47.17 ml, 630 mmol). The reaction mixture was allowed to warm to room temperature then stirred overnight. The solvent was removed by evaporation and the residue was redissolved in ethyl acetate, washed successively with 1M hydrochloric acid (400 ml) and brine (400 ml), dried over anhydrous sodium sulfate and filtered. The solution was concentrated under reduced pressure to leave the title compound as a colourless oil (28.11 g, 97%).

Step C: 3R-Isobutyl-2-methylene-succinic acid 1-benzyl ester 4-tert-butyl ester

3R-Isobutyl-2-methylene-succinic acid 4-tert-butyl ester (28.11 g, 122 mmol) was dissolved in acetone (500 ml) and the solution was placed under an argon atmosphere. Solid potassium carbonate (67.34 g, 488 mmol) was added and the

suspension was stirred for 30 minutes. Benzyl bromide (13.13 ml, 110 mmol) was added and the reaction mixture was left to stir overnight at room temperature. The inorganics were removed by filtration and the solvent was removed under reduced pressure to leave the title compound as a yellow oil

Step D: 3R-Isobutyl-2-methylene-succinic acid 1-benzyl ester

3R-Isobutyl-2-methylene-succinic acid 1-benzyl ester 4-tert-butyl ester (35.5 , 111 mmol) was deprotected by TFA acidolysis by the method described previously (Example 1, Step J). After 16 hours the solvents were removed by evaporation under reduced pressure and residual TFA was removed by azeotroping with toluene. The desired product was isolated as a yellow oil (32.5 g, including residual solvent).

Step E: 2-[3-Methyl-1R-(piperidine-1-carbonyl)-butyl]-acrylic acid benzyl ester

To a solution of 3R-Isobutyl-2-methylene-succinic acid 1-benzyl ester in ethyl acetate (500 ml) was added HOBt (14.99 g, 111 mmol) followed by EDC (21.31 g, 111 mmol). The solution was stirred for 1 hour at room temperature and piperidine (16.44 ml, 167 mmol) was added slowly. The reaction mixture was stirred for 3 days at room temperature, washed successively with 1M hydrochloric acid (500 ml), 1M sodium carbonate (500 ml) and brine (300 ml), dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated to leave an orange oil which was purified by flash chromatography (silica gel, ethyl acetate-hexane, 1:4) to afford the title compound as a yellow oil (19.3 g, 52%).

Step F: 5-Methyl-2S-methylaminomethyl-3R-(piperidine-1-carbonyl)-hexanoic acid benzyl ester

Methylamine (33% in methanol; 6.21 ml, 50 mmol) was added to a stirred solution of 2-[3-Methyl-1R-(piperidine-1-carbonyl)-butyl]-acrylic acid benzyl ester (8.3 g, 25 mmol) in methanol (50 ml) and the mixture was stirred at room temperature for 90

minutes. The solvent was removed *in vacuo* to leave the title compound as a yellow oil (15:1 mixture of diastereoisomers by ^{1}H-NMR) (8.865 g, 98%). .

Step G: 5-Methyl-2S-methylaminomethyl-3R-(piperidine-1-carbonyl)-hexanoic acid

The title compound was prepared by hydrogenolysis of the benzyl ester (550 mg, 1.52 mmol) by the method described earlier (Preparative Example A, Step E). The product was isolated as a white amorphous solid (410 mg, 99%).

Step H: 2S-{[(4-Methoxybenzenesulfonyl)-methyl-amino]-methyl}-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid

5-Methyl-2S-methylaminomethyl-3R-(piperidine-1-carbonyl)-hexanoic acid (1.51 mmol) was dissolved in dichloromethane (5 ml) and converted to the title sulfonamide by a similar method to that described previously (Example 1, Step I). The solution was washed with 1M hydrochloric acid (25 ml) and brine, dried over anhydrous magnesium sulfate and filtered. The desired product was isolated as a white foam (500 mg, 75%) on removal of the solvent.

Step I: 2S-{[(4-Methoxybenzenesulfonyl)-methyl-amino]-methyl}-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid hydroxyamide

2S-{[(4-Methoxybenzenesulfonyl)-methyl-amino]-methyl}-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid (500 mg, 1.13 mmol) was converted to the title hydroxamic acid by the procedure described in Example 1. The product was isolated as a white amorphous solid (26 mg, 5%) by flash chromatography (acid-washed silica gel, 3% methanol in dichloromethane). m.p. 147°C.

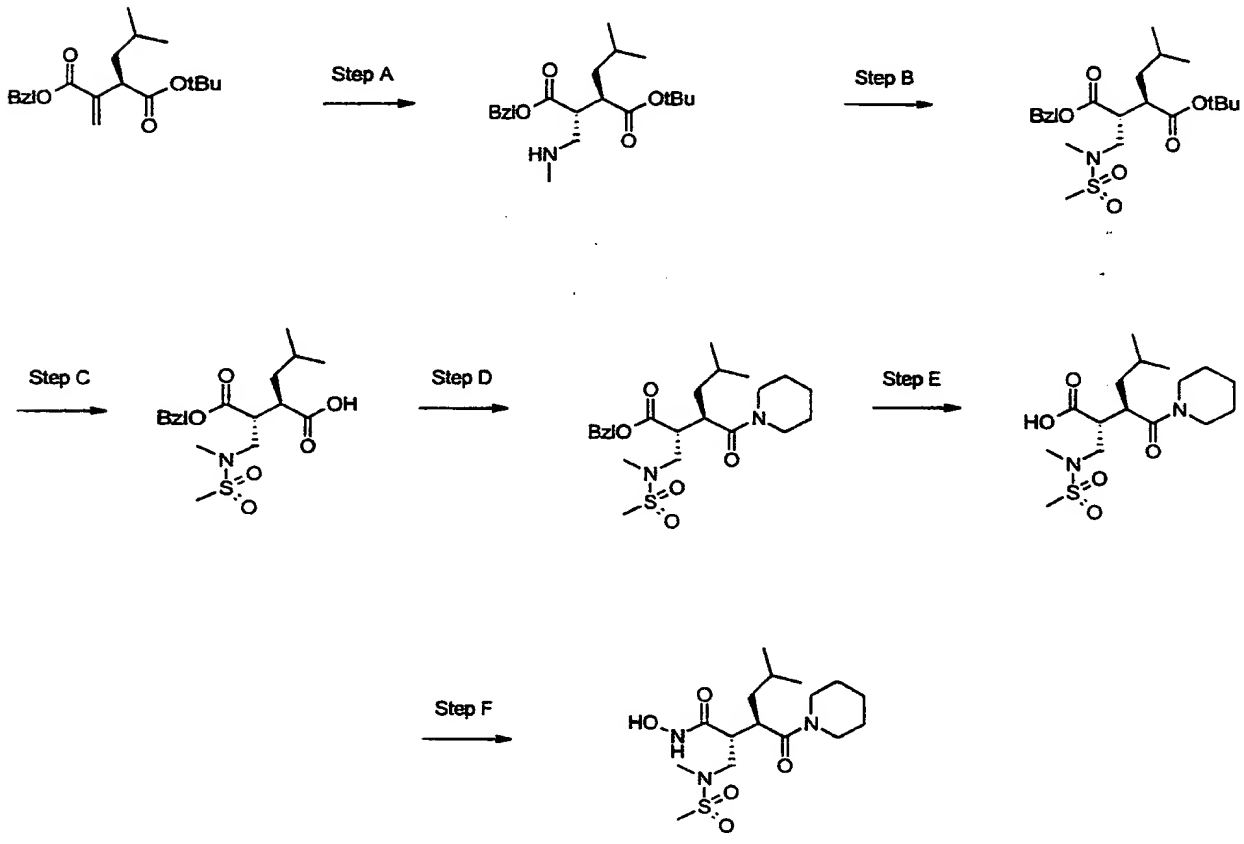
Preparative Example C

2S-[(Methanesulfonyl-methyl-amino)-methyl]-5-methyl-3R-(piperidine-1-carbonyl)-

hexanoic acid hydroxyamide

The title compound was prepared according to the route outlined in Scheme 3 and is summarised below.

Scheme 3



Reagents and conditions: (A) $MeNH_2$ in methanol; (B) MsCl, Et_3N, CH_2Cl_2; (C) TFA, CH_2Cl_2, 4°C; (D) piperidine, EDC, HOBt in EtOAc; (E) H_2, 10% Pd/C in EtOAc; (F) HOBt, EDC in DMF, then $H_2NOH.HCl$, NMM.

Step A: 3-Isobutyl-2-methylaminomethyl-succinic acid 1-benzyl ester 4-tert-butyl ester

3R-Isobutyl-2-methylene-succinic acid 1-benzyl ester 4-tert-butyl ester (Example 7, Step C) (10.0 g, 30.1 mmol) was dissolved in methanol (50 ml) and treated with methylamine (33% in methanol; 7.5 ml, 60.2 mmol) and the reaction mixture was stirred overnight at room temperature. The solvents were removed under reduced pressure to leave the title compound as an oil that was used without further purification.

Step B: 3R-Isobutyl-2-[(Methanesulfonyl)-methyl-amino)-methyl]-succinic acid 1-benzyl ester 4-tert-butyl ester

3-Isobutyl-2-methylaminomethyl-succinic acid 1-benzyl ester 4-tert-butyl ester (5.0 g, 13.8 mmol) was dissolved in dichloromethane and the solution was cooled in an ice bath. Triethylamine (3.9 ml, 28 mmol) was added dropwise followed by methanesulfonyl chloride (1.01 ml, 13.1 mmol) and the mixture was stirred at 0°C for 90 minutes, after which time a thick white precipitate had formed. The mixture was diluted with more dichloromethane (25 ml) and stirred overnight at room temperature. The suspension was washed successively with water, citric acid, sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to give the desired product (6.10 g, ca. quant.).

Step C: 3R-Isobutyl-2-[(Methanesulfonyl)-methyl-amino)-methyl]-succinic acid 1-benzyl ester

3R-Isobutyl-2-[(methanesulfonyl)-methyl-amino)-methyl]-succinic acid 1-benzyl ester 4-tert-butyl ester was converted to the title compound by acidolysis with TFA as described previously (Example 1, Step J).

Step D: 2S-[(Methanesulfonyl)-methyl-amino)-methyl]-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid benzyl ester

3R-Isobutyl-2-[(methanesulfonyl-amino)-methyl]-succinic acid 1-benzyl ester was coupled with piperidine under standard conditions (see Preparative Example A, Step G).

Step E: 2S-[(Methanesulfonyl)-methyl-amino)-methyl]-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid

The title compound was obtained by hydrogenolysis of the benzyl ester (method of Preparative Example A, Step E).

Step F: 2S-[(Methanesulfonyl)-methyl-amino)-methyl]-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid hydroxyamide

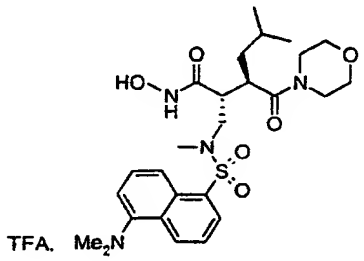
Hydroxylamine coupling of 2S-[(Methanesulfonyl)-methyl-amino)-methyl]-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid, according to the standard method (Example1, Step K), gave the title compound as a colourless oil.

The following compounds were prepared using the methods described in Preparative Example C, starting from 3R-isobutyl-2-methylene-succinic acid 1-benzyl ester 4-tert-butyl ester or 3R-cyclopentyl-2-methylene-succinic acid 1-benzyl ester 4-tert-butyl ester and the appropriate amines and sulfonamides. The products were purified by preparative HPLC.

Example 1

2S-{[(5-Dimethylaminonaphthalene-1-sulfonyl)-methyl-amino]-methyl}-5-methyl-3R-

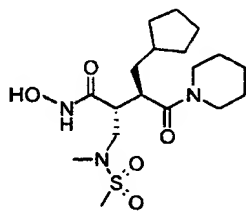
(morpholine-4-carbonyl)-hexanoic acid hydroxyamide (trifluoroacetic acid salt)



Yellow solid. m.p. 88 - 94°C. ^{1}H-NMR: δ (CD_3OD), 8.57 (1H, d, J = 9.0 Hz), 8.54 (1H, d, J = 8.8 Hz), 8.16 (1H, d, J = 7.4 Hz), 7.67 (2H, m), 7.47 (1H, d, J = 7.7 Hz), 3.73 - 3.37 (8H, br m), 3.14 - 2.82 (3H, m), 3.02 (6H, s), 2.75 (3H, s), 2.69 (1H, m), 1.64 (1H, m), 1.36 (1H, m), 1.18 (1H, m) and 0.86 (6H, d, J = 6.5 Hz). ^{13}C-NMR: δ (CD_3OD), 174.8, 171.1, 135.4, 131.9, 131.6, 131.0, 129.7, 125.6, 123.1, 117.9, 68.2, 52.0, 48.3, 46.6, 44.1, 42.5, 40.3, 36.8, 27.4, 24.6 and 22.7. IR: ν_{max} 2959, 2358, 1675, 1614, 1456, 1332, 1140, 1042, 966, 795, 723, 622 and 578 cm^{-1}. Found: C 49.68% H 5.93% N 8.23%; $C_{28}H_{39}N_4O_8SF_3$. 1.6 H_2O requires 49.64% H 6.26% N 8.27%.

Example 2

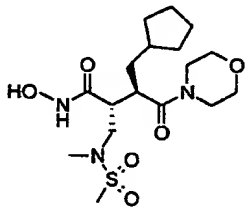
3R-Cyclopentylmethyl-N-hydroxy-2S-[(methanesulfonyl-methyl-amino)-methyl)]-4-oxo-4-piperidin-1-yl-butyramide



White foam. m.p. 78-80°C. ^{1}H-NMR: δ (CD_3OD), 3.57 (4H, m), 3.40 (1H, dd, J=10.1, 13.5Hz), 3.31 (1H, m), 2.97 (1H, dd, J=4.4, 13.5Hz), 2.82 (3H, s), 2.79 (3H, s), 2.67 (1H, m), 1.55 (14H, br m), 1.35 (1H, m) and 1.10 (2H, m). ^{13}C-NMR: δ (CD_3OD), 174.3, 171.7, 52.1, 48.4, 46.2, 44.8, 41.9, 39.7, 39.2, 36.4, 36.0, 35.4, 34.2, 28.3, 27.3, 26.6 and 25.9. IR: ν_{max} (reflection disc) 3193, 2943, 1778, 1713, 1663, 1601, 1449, 1331, 1154, 1022 and 967 cm^{-1}. $C_{18}H_{33}N_3O_5S$ (403.5); MS (electrospray): 404.4 $[M+H]^+$, 426.2 $[M+Na]^+$.

Example 3

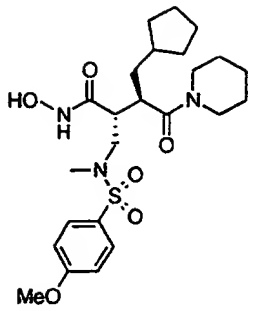
3R-Cyclopentylmethyl-N-hydroxy-2S-[(methanesulfonyl-methyl-amino)-methyl]-4-morpholin-4-yl-4-oxo-butyramide



White foam. m.p. 82 - 84°C. ^{1}H-NMR: δ (CD_3OD), 3.71 (8H, br m), 3.32 (1H, m), 3.10 (2H, m), 2.82 (3H, s), 2.78 (3H, s), 2.71 (1H, m), 1.58 (8H, br m), 1.34 (1H, m) and 1.10 (2H, m). ^{13}C-NMR: δ (CD_3OD), 173.2, 169.9, 66.5, 50.5, 46.6, 42.4, 39.7, 38.0, 37.3, 34.3, 33.3, 32.0 and 24.8. IR: ν_{max} 3218, 2944, 2870, 1774, 1611, 1451, 1327, 1153, 1036 and 967cm^{-1}.

Example 4

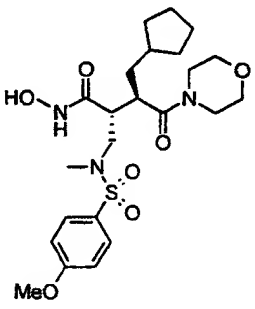
3R-Cyclopentylmethyl-N-hydroxy-2S-{[(4-benzenesulfonyl)-methyl-amino]-methyl}-4-oxo-4-piperidine-1-yl-butyramide



White foam. m.p. 64 - 65°C. ^{1}H-NMR: δ (CD_3OD), 7.69 (2H, d, J = 8.9 Hz), 7.10 (2H, d, J=8.9 Hz), 3.87 (3H, s), 3.70 (2H, m), 3.47 (2H, m), 3.17 (2H, m), 2.64 (3H, s), 2.61 (2H, m) and 1.76 - 1.06 (17H, br m). ^{13}C-NMR: δ (CD_3OD), 174.3, 171.6, 165.3, 131.3, 129.4, 115.9, 56.7, 52.8, 48.7, 48.3, 44.7, 41.5, 39.7, 39.1, 37.1, 35.0, 33.7, 28.4, 27.3, 26.6 and 25.8. IR ν_{max} 3200, 2942, 2862, 1777, 1598, 1498, 1454, 1343, 1261, 1161 and 1024 cm^{-1}.

Example 5

3R-Cyclopentylmethyl-N-hydroxy-2S-{[(4-benzenesulfonyl)-methyl-amino]-methyl}-4-morpholin-4-yl-4-oxo-butyramide

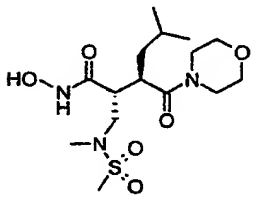


White foam. m.p. 71 - 72° ^{1}H-NMR: δ (CD_3OD), 7.70 (2H, d, J = 8.9 Hz), 7.11 (2H, d, J = 8.9 Hz), 3.88 (3H, s), 3.63 (8H, br m), 3.11 (2H, m), 2.85 (1H, m), 2.72 (1H, m), 2.62 (3H, s) and 1.78 - 1.09 (11H, br m). ^{13}C-NMR: δ (CD_3OD), 174.9,

171.5, 165.3, 131.3, 129.4, 115.9, 68.2, 56.7, 52.9, 48.1, 44.1, 41.5, 39.7, 39.0, 37.1, 35.0, 33.7 and 26.6. IR: ν_{max} 3207, 2950, 1909, 1778, 1603, 1462, 1343, 1264, 1164, 1117, 1027 and 944 cm^{-1}.

Example 6

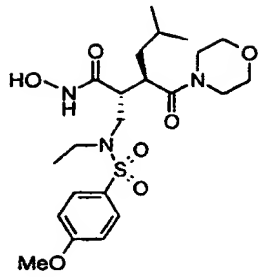
2S-[(Methanesulfonyl-methyl-amino)-methyl]-5-methyl-3R-(morpholine-4-carbonyl)-hexanoic acid hydroxyamide



White foam. m.p. 75 - 78°C. ^{1}H-NMR: δ (CD_3OD), 3.82 - 3.62 (8H, m), 3.43 - 3.35 (1H, m), 3.21 - 3.10 (2H, m), 2.85 (3H, s), 2.82 (3H, s), 2.75 - 2.65 (1H, m), 1.74 - 1.63 (1H, m), 1.50 - 1.37 (1H, m), 1.29 - 1.18 (1H, m), 0.92 (3H, d, J = 6.4 Hz) and 0.91 (3H, d, J = 6.5 Hz). ^{13}C-NMR: δ (CD_3OD), 174.9, 171.5, 68.2, 52.2, 48.3, 44.1, 42.6, 40.3, 36.1, 27.3, 24.7 and 22.7. IR: ν_{max} 3224, 2959, 1735, 1614, 1446, 1387, 1328, 1267, 1243, 1153, 1116, 1068, 1040, 965, 782, 575 and 519 cm^{-1}.

Example 7

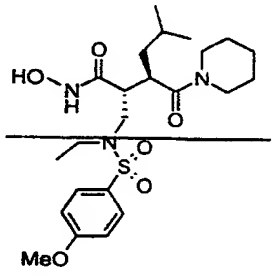
2S-{[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-methyl}-5-methyl-3R-(morpholine-4-carbonyl)-hexanoic acid hydroxyamide



White foam. m.p. 87 - 89°C. ^{1}H-NMR: δ ($CDCl_3$), 10.26 (1H, br s), 7.72 (2H, d, J = 8.9 Hz), 6.98 (2H, d, J = 8.9 Hz), 3.86 (3H, s), 3.73 - 3.59 (8H, m), 3.31 - 3.12 (4H, m), 3.10 - 2.96 (2H, m), 1.77 - 1.66 (1H, m), 1.50 - 1.37 (1H, m), 1.31 - 1.21 (1H, m), 0.98 (3H, t, J = 7.1 Hz), 0.89 (3H, d, J = 6.4 Hz) and 0.88 (3H, d, J = 6.4 Hz). ^{13}C-NMR: δ ($CDCl_3$), 174.3, 169.9, 163.5, 130.2, 130.0, 114.8, 67.3, 67.2, 56.0, 48.3, 47.2, 46.2, 45.0, 42.9, 40.1, 37.9, 26.5, 24.0, 22.5 and 13.7. IR: ν_{max} 3229, 2959, 1612, 1496, 1463, 1386, 1336, 1303, 1260, 1182, 1154, 1092, 1067, 1024, 892, 838, 804, 730 and 560 cm^{-1}. Found: C 53.47% H 7.22% N 8.49%; $C_{22}H_{35}N_3O_7S$. 0.5 H_2O requires C 53.42% H 7.34% N 8.50%.

Example 8

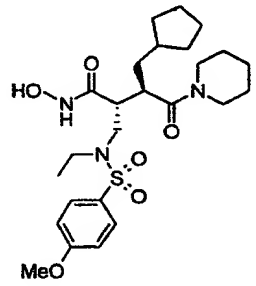
2S-{[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-methyl}-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid hydroxyamide



White foam. m.p. 88.5 - 90°C. ^{1}H-NMR: δ ($CDCl_3$), 10.32 (1H, br s), 7.74 (2H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.9 Hz), 3.86 (3H, s), 3.62 - 3.60 (4H, m), 3.36 - 3.19 (4H, m), 3.12 - 2.93 (2H, m), 1.74 - 1.37 (8H, m), 1.28 - 1.18 (1H, m), 0.99 (3H, t, J = 7.2 Hz), 0.90 (3H, d, J = 6.1 Hz) and 0.88 (3H, d, J = 6.2 Hz). ^{13}C-NMR: δ ($CDCl_3$), 175.7, 172.0, 165.2, 132.2, 131.9, 116.5, 57.9, 50.3, 49.6, 47.8, 46.9, 45.5, 41.7, 39.6, 29.0, 28.3, 28.0, 26.7, 25.9, 24.4 and 15.7. IR: ν_{max} 3206, 2937, 1597, 1496, 1451, 1336, 1257, 1182, 1153, 1022, 836, 804 and 729 cm^{-1}. Found: C 56.41% H 7.69% N 8.54%; $C_{23}H_{37}N_3O_6S$. 0.3 H_2O requires C 56.49% H 7.75% N 8.59%.

Example 9

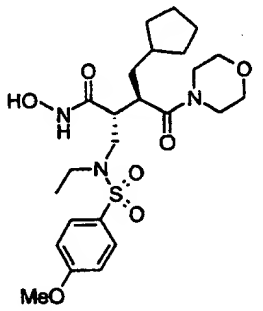
3R-Cyclopentylmethyl-2S-{[ethyl-(4-methoxy-benzenesulfonyl)-amino]-methyl}-N-hydroxy-4-oxo-4-morpholine-1-yl-butyramide



White foam. ^{1}H-NMR: δ (CD_3OD), 7.74 (2H, d, J = 8.9 Hz), 7.06 (2H, d, J = 8.9 Hz), 3.87 (3H, s), 3.71 (2H, m), 3.52 (2H, m), 3.30 - 2.91 (5H, m), 2.72 (1H, m), 1.87 - 1.38 (14H, m), 1.32 (1H, m) and 1.00 (6H, m). ^{13}C-NMR: δ (CD_3OD), 174.0, 171.4, 164.8, 131.6, 130.7, 115.5, 56.3, 48.0, 45.4, 44.4, 39.4, 38.8, 34.6, 33.4, 28.1, 27.1, 26.2, 25.5 and 13.4. IR: ν_{max} 3211, 2948, 1736, 1598, 1497, 1453, 1335, 1261, 1156, 1093 and 1024 cm^{-1}. $C_{25}H_{39}N_3O_6S$ (509.7); MS (electrospray): 510.4 $[M+H]^+$, 532.2 $[M+Na]^+$.

Example 10

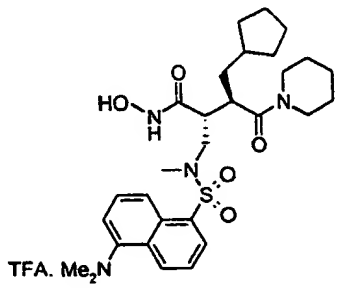
3R-Cyclopentylmethyl-2S-{[ethyl-(4-methoxy-benzenesulfonyl)-amino]-methyl}-N-hydroxy-4-morpholine-4-yl-4-oxo-butyramide



White foam. ^{1}H-NMR: δ (CD_3OD), 7.72 (2H, d, J = 8.9 Hz), 7.08 (2H, d, J = 8.9 Hz), 3.87 (3H, s), 3.65 (10H, br m), 3.21 (1H, m), 3.05 (1H, m), 2.89 (1H, m), 2.78 (1H, m), 1.89 - 1.49 (8H, br m), 1.39 (1H, m), 1.10 (2H, m) and 0.98 (3H, t, J = 7.1 Hz). ^{13}C-NMR: δ (CD_3OD), 174.9, 171.6, 165.2, 131.9, 131.6, 115.9, 68.4, 56.7, 48.7, 45.4, 44.2, 39.6, 39.1, 35.0, 33.7, 26.6 and 13.7. IR: ν_{max} 3228, 2952, 2862, 1778, 1600, 1497, 1463, 1340, 1263, 1160, 1115 and 1027cm^{-1}.

Example 11

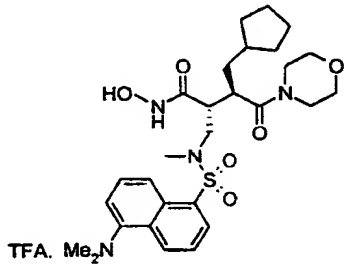
3R-Cyclopentylmethyl-2S-{[(5-dimethyamino-naphthalene-1-sulfonyl)-methyl-amino]-methyl}-N-hydroxy-4-oxo-4-piperidine-1-yl-butyramide (trifluoroacetic acid salt)



Yellow foam. ^{1}H-NMR: δ (CD_3OD), 8.57 (1H, d, J = 8.6 Hz), 8.51 (1H, d, J = 8.7 Hz), 8.14 (1H, d, J = 7.4 Hz), 7.65 (2H, m), 7.45 (1H, d, J = 7.4 Hz), 3.65 (4H, m), 3.42 (1H, m), 3.08 (1H, m), 3.01 (6H, s), 2.75 (3H, s), 2.71 (2H, m), 1.59 (13H, br m), 1.28 (2H, m) and 1.01 (2H, m). ^{13}C-NMR: δ (CD_3OD), 174.2, 171.5, 150.9, 135.2, 132.0, 131.0, 129.7, 125.5, 123.0, 117.8, 52.1, 48.6, 48.4, 46.6, 44.7, 41.5, 39.6, 39.1, 36.6, 35.0, 33.7, 28.3, 27.3, 26.4 and 22.6. IR: ν_{max} 3202, 2944, 1606, 1454, 1332, 1249, 1141, 1048, 1024, 946 and 796 cm^{-1}. $C_{29}H_{43}N_4O_5S.C_2F_3O_2$ (558.7); MS (electrospray): 559.4 $[M+H]^+$.

Example 12

3R-Cyclopentylmethyl-2S-{[(5-dimethyamino-naphthalene-1-sulfonyl)-methyl-amino]-methyl}-N-hydroxy-4-morpholine-4-yl-4-oxo-butyramide trifluoroacetic acid salt

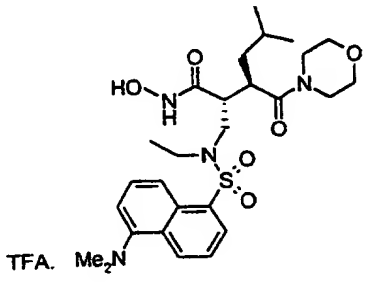


Yellow foam. ^{1}H-NMR: δ (CD_3OD), 8.56 (1H, d, J = 4.5 Hz), 8.54 (1H, d, J = 4.6 Hz), 8.14 (1H, d, J = 6.3 Hz), 7.68 (2H, m), 7.49 (1H, d, J = 7.5 Hz), 3.61 (8H, m), 3.41 (1H, m), 3.04 (7H, m), 2.91 (1H, m), 2.75 (4H, m), 1.65 (8H, br m), 1.31 (1H, m) and 1.01 (2H, m).^{13}C-NMR: δ (CD_3OD), 174.8, 171.4, 150.5, 135.2, 132.0, 131.9, 130.9, 129.7, 125.7, 123.3, 118.0, 68.3, 52.1, 48.4, 46.7, 44.1, 41.5, 39.6, 39.0, 36.7, 35.0, 33.7 and 26.6. IR: ν_{max} 3207, 2943, 2862, 1636, 1516, 1458, 1333, 1267, 1140, 1042, 946 and 796 cm^{-1}. Found C 53.54% H 6.11% N 8.33%. $C_{30}H_{41}F_3N_4O_8S$

requires C 55.35% H 6.44% N 8.33%.

Example 13

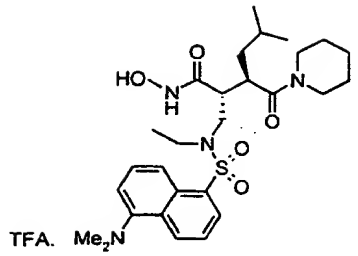
2S-{[(5-Dimethylaminonaphthalene-1-sulfonyl)-ethyl-amino]-methyl}-5-methyl-3R-(morpholine-4-carbonyl)-hexanoic acid hydroxyamide (trifluoroacetic acid salt)



Yellow foam. ^{1}H-NMR: δ (CD_3OD), 8.60 (1H, d, J = 8.5 Hz), 8.40 (1H, d, J = 8.7 Hz), 8.22 (1H, d, J = 8.5 Hz), 7.65 (2H, dd, J = 8.6, 7.5 Hz), 7.38 (1H, d, J=7.3 Hz), 3.75 - 3.24 (11H, m), 3.18 - 3.00 (2H, m), 2.97 (6H, s), 2.79 - 2.70 (1H, m), 1.75 - 1.64 (1H, m), 1.45 - 1.32 (1H, m), 1.23 - 1.13 (1H, m) and 0.91 - 0.81 (9H, m). ^{13}C-NMR: δ (CD_3OD), 174.7, 171.5, 152.3, 136.6, 131.8, 131.5, 131.4, 129.7, 125.2, 122.0, 117.4, 68.3, 48.8, 46.4, 44.2, 44.0, 42.3, 40.5, 27.4, 24.6, 22.6 and 13.2. IR: ν_{max} 3194, 2955, 1609, 1458, 1319, 1267, 1198, 1139, 1042, 932, 892, 794, 717 cm^{-1}.

Example 14

2S-{[(5-Dimethylaminonaphthalene-1-sulfonyl)-methyl-amino]-methyl}-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid hydroxyamide (trifluoroacetic acid salt)

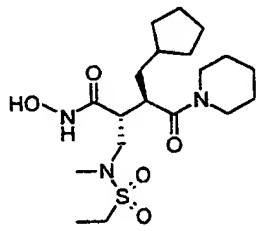


Yellow foam. ^{1}H-NMR: δ (CD_3OD), 8.60 (1H, d, J = 8.5 Hz), 8.39 (1H, d, J = 8.7 Hz), 8.22 (1H, d, J = 8.5 Hz), 7.67 - 7.61 (2H, m), 7.38 (1H, d, J = 7.5 Hz), 3.75 - 3.41 (6H, m), 3.31 - 3.03 (3H, m), 2.96 (6H, s), 2.77 - 2.67 (1H, m), 1.73 - 1.33 (8H, m), 1.21 - 1.10 (1H, m) and 0.90 - 0.83 (9H, m). ^{13}C-NMR: δ (CD_3OD), 174.2, 171.6, 136.6, 131.8, 131.5, 129.6, 125.2, 117.3, 111.4, 44.0, 42.4, 41.5, 40.0, 26.0, 25.1, 23.5, 22.3, 20.3 and 10.8. IR: ν_{max} 3359, 3360, 3198, 2938, 1777, 1642, 1606, 1465, 1389, 1322, 1251, 1227, 1199, 1140, 1056, 1019, 989, 931 cm^{-1}. Found: C 58.55% H 7.62% N 9.69%; $C_{30}H_{42}N_4O_7SF_3$. 1.5 H_2O requires C 58.62% H 7.91% N 9.76%.

The following additional compounds were prepared from 2-[2-cyclopentyl-1R-(piperidine-1-carbonyl)-ethyl]-acrylic acid benzyl ester by parallel synthesis in solution using the methods described in Preparative Example B. Briefly, Michael addition of the appropriate amine was followed by sulfonylation with the desired sulfonyl chloride, catalytic transfer hydrogenolysis (4.4% formic acid in methanol, 10% palladium on carbon, room temperature, 4 hours) and direct hydroxylamine coupling. The products were generally isolated in 90-95% purity by preparative reverse phase HPLC and characterised by electrospray mass spectrometry.

Example 15

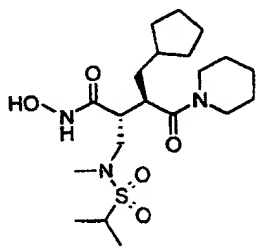
3R-Cyclopentylmethyl-2S-[(ethanesulfonyl-methyl-amino)-methyl]-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide



$C_{20}H_{37}N_3O_4S$ (415.6); MS (electrospray): 416.6 $[M+H]^+$, 438.6 $[M+Na]^+$.

Example 16

3R-Cyclopentylmethyl-N-hydroxy-2S-{[methyl-(propane-2-sulfonyl]-amino]-methyl}-4-oxo-4-piperidin-1-yl-butyramide

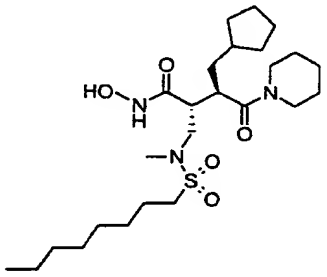


$C_{21}H_{39}N_3O_4S$ (429.6); MS (electrospray): 430.6 $[M+H]^+$, 452.6 $[M+Na]^+$.

Example 17

3R-Cyclopentylmethyl-N-hydroxy-2S-{[methyl-(octane-1-sulfonyl)-amino]-methyl}-4-

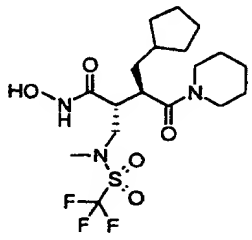
oxo-4-piperidin-1-yl-butyramide



$C_{26}H_{49}N_3O_4S$ (499.8): MS (electrospray): 500.8 $[M+H]^+$, 522.8 $[M+Na]^+$.

Example 18

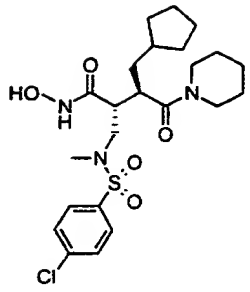
3R-Cyclopentylmethyl-N-hydroxy-2S-[(methyl-trifluoromethanesulfonyl-amino)-methyl]-4-oxo-4-piperidin-1-yl-butyramide



$C_{19}H_{32}F_3N_3O_4S$ (455.5); MS (electrospray): 456.5 $[M+H]^+$, 478.5 $[M+Na]^+$.

Example 19

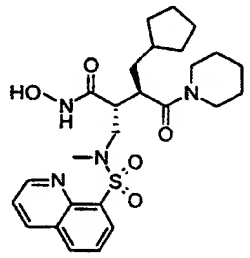
2S-{[(4-Chloro-benzenesulfonyl)-methyl-amino]methyl}-3R-cyclopentylmethyl-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide



$C_{24}H_{36}ClN_3O_4S$ (498.1); MS (electrospray): 499.1, 501.1 $[M+H]^+$, 521.1, 523.1 $[M+Na]^+$.

Example 20

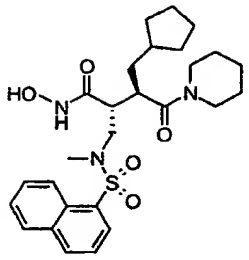
3R-Cyclopentylmethyl-N-hydroxy-2S-{[methyl-(quinoline-8-sulfonyl)-amino]-methyl}-4-oxo-4-piperidin-1-yl-butyramide



$C_{27}H_{38}N_4O_4S$ (514.7); MS (electrospray): 515.7 $[M+H]^+$, 537.7 $[M+Na]^+$.

Example 21

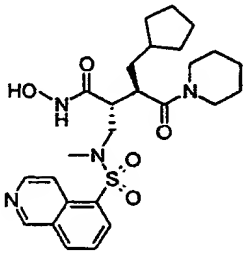
3R-Cyclopentylmethyl-N-hydroxy-2S-{[methyl-(naphthalene-1-sulfonyl)-amino]-methyl}-4-oxo-4-piperidin-1-yl-butyramide



$C_{28}H_{39}N_3O_4S$ (513.7); MS (electrospray): 514.7 $[M+H]^+$, 536.7 $[M+Na]^+$.

Example 22

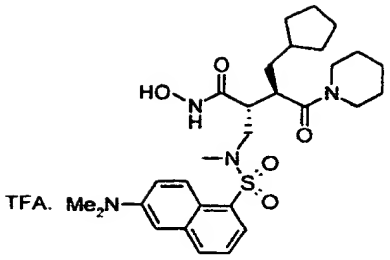
3R-Cyclopentylmethyl-N-hydroxy-2S-{[(isoquinoline-5-sulfonyl)-methyl-amino]-methyl}-4-oxo-4-piperidin-1-yl-butyramide



$C_{27}H_{38}N_4O_4S$ (514.7); MS (electrospray): 515.7 $[M+H]^+$, 537.7 $[M+Na]^+$.

Example 23

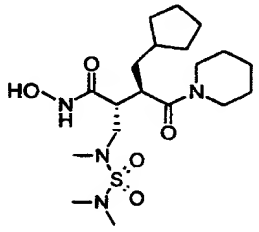
3R-Cyclopentylmethyl-2S-{[(6-dimethylamino-naphthalene-1-sulfonyl)-methyl-amino]-methyl}-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide



$C_{30}H_{45}N_4O_4S$. $C_2F_3O_2$ (556.8); MS (electrospray): 557.8 $[M+H]^+$.

Example 24

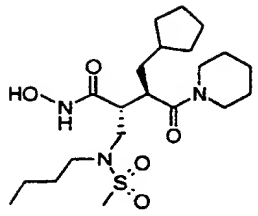
3R-Cyclopentylmethyl-2S-{[dimethylsulfamoyl-methyl-amino]-methyl}-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide



$C_{20}H_{38}N_4O_4S$ (430.6); MS (electrospray): 431.6 $[M+H]^+$, 453.6 $[M+Na]^+$

Example 25

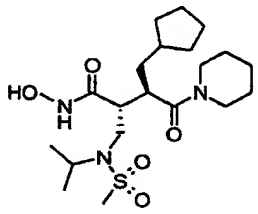
2S-[(Butyl-methanesulfonyl-amino)-methyl]-3R-cyclopentylmethyl-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide



$C_{22}H_{41}N_3O_4S$ (443.7); MS (electrospray): 444.7 $[M+H]^+$, 466.7 $[M+Na]^+$.

Example 26

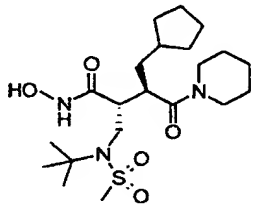
3R-Cyclopentylmethyl-N-hydroxy-2S-[(isopropyl-methanesulfonyl)-amino)-methyl]-4-oxo-4-piperidin-1-yl-butyramide



$C_{21}H_{39}N_3O_4S$ (429.6); MS (electrospray): 430.6 $[M+H]^+$, 452.6 $[M+Na]^+$.

Example 27

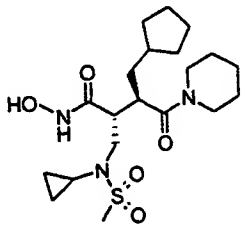
2S-[(*tert*-Butyl-methanesulfonyl)-amino)-methyl]-3R-cyclopentylmethyl-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide



$C_{22}H_{41}N_3O_4S$ (443.7); MS (electrospray): 444.7 $[M+H]^+$, 466.7 $[M+Na]^+$.

Example 28

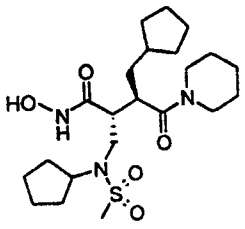
3R-Cyclopentylmethyl-N-hydroxy-2S-[(cyclopropyl-methanesulfonyl)-amino)-methyl]-4-oxo-4-piperidin-1-yl-butyramide



$C_{21}H_{37}N_3O_4S$ (427.6); MS (electrospray): 428.6 $[M+H]^+$, 450.6 $[M+Na]^+$.

Example 29

2S-[(Cyclopentyl-methanesulfonyl)-amino)-methyl]-3R-cyclopentylmethyl-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide



$C_{23}H_{41}N_3O_4S$ (455.7); MS (electrospray): 456.7 $[M+H]^+$, 478.7 $[M+Na]^+$.

Biological Example A

The potency of compounds of the present invention as inhibitors of human fibroblast collagenase may be determined by the procedure of Cawston and Barrett, (Anal. Biochem., 99, 340-345, 1979), hereby incorporated by reference, whereby a 1mM solution of the compound being tested, or a dilution thereof, was incubated at 37°C for 16 hours with collagen and human fibroblast collagenase (buffered with 25mM Hepes, pH 7.5 containing 5mM $CaCl_2$, 0.05% Brij 35 and 0.02% NaN_3). The collagen was acetylated ^{14}C collagen prepared by the method of Cawston and Murphy, (*Methods in Enzymology*, 80, 711, 1981), hereby incorporated by reference. The samples were centrifuged to sediment undigested collagen, and an aliquot of the radioactive supernatant removed for assay on a scintillation counter as a measure of hydrolysis. The collagenase activity in the presence of 1mM of the test compound, or a dilution thereof, was compared to activity in a control devoid of inhibitor and the result reported below as that of inhibitor concentration effecting 50% inhibition of the collagenase activity (IC_{50}). Compounds of the invention tested in this assay were shown to be active as inhibitors of human fibroblast collagenase.

CLAIMS:

1. A compound which is a member of the group consisting o:

2S-{[(5-Dimethylaminonaphthalene-1-sulfonyl)-methyl-amino]-methyl}-5-methyl-3R-(morpholine-4-carbonyl)-hexanoic acid hydroxyamide

3R-Cyclopentylmethyl-N-hydroxy-2S-[(methanesulfonyl-methyl-amino)-methyl)]-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-[(methanesulfonyl-methyl-amino)-methyl)]-4-morpholin-4-yl-4-oxo-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-{[(4-benzenesulfonyl)-methyl-amino]-methyl}-4-oxo-4-piperidine-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-{[(4-benzenesulfonyl)-methyl-amino]-methyl}-4-morpholin-4-yl-4-oxo-butyramide

2S-[(Methanesulfonyl-methyl-amino)-methyl]-5-methyl-3R-(morpholine-4-carbonyl)-hexanoic acid hydroxyamide

2S-{[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-methyl}-5-methyl-3R-(morpholine-4-carbonyl)-hexanoic acid hydroxyamide

2S-{[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-methyl}-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid hydroxyamide

3R-Cyclopentylmethyl-2S-{[ethyl-(4-methoxy-benzenesulfonyl)-amino]-methyl}-N-hydroxy-4-oxo-4-morpholine-1-yl-butyramide

3R-Cyclopentylmethyl-2S-{[ethyl-(4-methoxy-benzenesulfonyl)-amino]-methyl}-N-hydroxy-4-morpholine-4-yl-4-oxo-butyramide

3R-Cyclopentylmethyl-2S-{[(5-dimethyamino-naphthalene-1-sulfonyl)-methyl-amino]-methyl}-N-hydroxy-4-oxo-4-piperidine-1-yl-butyramide

3R-Cyclopentylmethyl-2S-{[(5-dimethyamino-naphthalene-1-sulfonyl)-methyl-amino]-methyl}-N-hydroxy-4-morpholine-4-yl-4-oxo-butyramide

2S-{[(5-Dimethylaminonaphthalene-1-sulfonyl)-ethyl-amino]-methyl}-5-methyl-3R-(morpholine-4-carbonyl)-hexanoic acid hydroxyamide

2S-{[(5-Dimethylaminonaphthalene-1-sulfonyl)-methyl-amino]-methyl}-5-methyl-3R-(piperidine-1-carbonyl)-hexanoic acid hydroxyamide

3R-Cyclopentylmethyl-2S-[(ethanesulfonyl-methyl-amino)-methyl]-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-{[methyl-(propane-2-sulfonyl]-amino]-methyl}-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-{[methyl-(octane-1-sulfonyl)-amino]-methyl}-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-[(methyl-trifluoromethanesulfonyl-amino)-methyl]-4-oxo-4-piperidin-1-yl-butyramide

2S-{[(4-Chloro-benzenesulfonyl)-methyl-amino]methyl}-3R-cyclopentylmethyl-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-{[methyl-(quinoline-8-sulfonyl)-amino]-

methyl}-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-{[methyl-(naphthalene-1-sulfonyl)-amino]-methyl}-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-{[(isoquinoline-5-sulfonyl)-methyl-amino]-methyl}-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-2S-{[(6-dimethylamino-naphthalene-1-sulfonyl)-methyl-amino]-methyl}-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-2S-{[dimethylsulfamoyl-methyl-amino]-methyl}-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide

2S-[(Butyl-methanesulfonyl-amino)-methyl]-3R-cyclopentylmethyl-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-[(isopropyl-methanesulfonyl)-amino)-methyl]-4-oxo-4-piperidin-1-yl-butyramide

2S-[(*tert*-Butyl-methanesulfonyl)-amino)-methyl]-3R-cyclopentylmethyl-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide

3R-Cyclopentylmethyl-N-hydroxy-2S-[(cyclopropyl-methanesulfonyl)-amino)-methyl]-4-oxo-4-piperidin-1-yl-butyramide

2S-[(Cyclopentyl-methanesulfonyl)-amino)-methyl]-3R-cyclopentylmethyl-N-hydroxy-4-oxo-4-piperidin-1-yl-butyramide

and pharmaceutically acceptable salts hydrates and solvates thereof.

2. A pharmaceutical or veterinary composition comprising a compound as claimed in claim 1 or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof, together with a pharmaceutically or veterinarily acceptable excipient or carrier.

3. The use of a compound as claimed in claim 1 in the preparation of an agent for the treatment of conditions or diseases mediated by MMPs

4. A method of management of diseases or conditions mediated by MMPs, which method comprises administering to the mammal an effective dose of a compound as claimed in claim 1.

5. A use as claimed in claim 3 or a method as claimed in claim 4, wherein the disease or condition is rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, cancer, or a neuroinflammatory disorder.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/GB 98/00914

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/18 A61K31/435

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 33731 A (HOFFMANN LA ROCHE ;BROADHURST MICHAEL JOHN (GB); BROWN PAUL ANTHON) 14 December 1995 ---	1-5
A	EP 0 574 758 A (HOFFMANN LA ROCHE) 22 December 1993 ---	1-5
E	WO 98 17655 A (BRITISH BIOTECH PHARMACEUTICALS LTD., UK;BECKETT, RAYMOND PAUL; MARTIN) 30 April 1998 cited in the application see claims -----	1-5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
13 November 1998	25/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pauwels, G

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

.ernational application No.
PCT/GB 98/00914

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 4
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 4 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

.nformation on patent family members

Int· ·ional Application No
PCT/GB 98/00914

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9533731 A	14-12-1995	AU 2615695 A	04-01-1996
EP 0574758 A	22-12-1993	AT 170840 T	15-09-1998
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WO 9817655 A	30-04-1998	AU 4714297 A	15-05-1998
		GB 2324091 A	14-10-1998